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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Examining the Role of Toxic Tau Proteins in Alzheimer's Disease

Dr. Wilner:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and joining me today to discuss his research on toxic tau proteins in Alzheimer's disease is Dr. George Bloom. Dr. Bloom is a Professor of Biology, Cell Biology, and Neuroscience at the University of Virginia.

Dr. Bloom, it's great to have you with us today.

Dr. Bloom:
Pleasure to be here. Thanks for inviting me, Andrew.

Dr. Wilner:
Let's start with some background, Dr. Bloom. Please explain the role of tau proteins in the normal functioning of the brain and how they become toxic in the context of Alzheimer's disease.

Dr. Bloom:
Arguably, the best-known function of tau in normal brain is to regulate the assembly of microtubules and neurons, especially in axons, but it does perform a number of other important roles. It has some still pretty mysterious roles in regulating gene expression and also regulating the activity of NMDA receptors and possibly other neurotransmitter receptors as well.

Tau is what's known as an intrinsically misfolded protein, so it has very little stable structure. For those of you who know a little bit about protein structure, it has no secondary structure, no stable alpha helical or beta sheet structure, but it does have some semi-stable tertiary structure that causes the N-terminus, the amino terminus of the protein, to reside very close to the C-terminus, the carboxy terminus of the protein, so it folds sort of like a hairpin. And one of the things that happens in Alzheimer's disease and in a lot of other neurodegenerative diseases as well is that this tertiary structure falls apart, so tau unfolds, and that, among other things, seems to reduce the affinity of tau for microtubules and promote the aggregation of tau first into small aggregates called oligomers, and eventually into the kind of filaments that accumulate in neurofibrillary tangles, one of the histopathological hallmarks of Alzheimer's disease as well as a number of other diseases known as tauopathies.

Dr. Wilner:
So are there any known risk factors or genetic predispositions that make some people more susceptible to the increase of toxic tau in the brain?

Dr. Bloom:
Well, one of the things that my lab has been studying for many years is toxic signaling from amyloid beta, which is the peptide that forms plaques to tau. And that buildup of amyloid beta or A beta in the brain is usually not good for you, but most of the bad things that amyloid beta seems to do occur by mechanisms that absolutely require tau.

So what is the connection? Well, there's a lot that we don't know, but what we do know is that when amyloid beta builds up to a certain level and the right varieties of amyloid beta peptides present in the brain, they activate a number of protein kinases that then phosphorylate tau at many sites, and in a general sense, that's really required for the conversion of normal tau into pathological tau. And then the tau itself is at least directly responsible for damaging and destroying synapses and killing neurons, so these effects of amyloid beta are largely indirect occurring through tau that gets modified in consequence to the buildup of A beta.

Dr. Wilner:

Now we do have scans that measure the amount of amyloid in the brain. What about tau? Can we scan a patient for tau?

Dr. Bloom:
There are, I believe, two FDA-approved PET ligands for tau now, and they are widely used along with the PET methods, the PET ligands for plaques. So these PET ligands pick up neurofibrillary tangles. They don't pick up soluble forms of tau, nor is there any evidence that they can detect improperly misfolded tau and small aggregates of tau that are toxic but haven't formed filaments yet.

Dr. Wilner:
So the PET scans measure tau, but they don't differentiate between normal tau and pathological tau? They just tell you how?

Dr. Bloom:
No, they can only detect tau that's in the form of filaments. But it's actually the small aggregates of misfolded tau oligomers that are far more toxic than the tau that's ensconced in these much less soluble filaments, and these soluble oligomers of tau are floating around inside neurons and are passed from neuron to neuron and start damaging synapses and doing a whole lot of other things as we're discovering, none of them very good quite a long time before you see tangles.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. George Bloom about toxic tau proteins in Alzheimer's disease.

Now, as I understand it, Dr. Bloom, you and your team discovered that tau oligomers—and you mentioned that earlier—can affect normally smooth shape of neuronal nuclei. So help me with that. What's an oligomer, and why does it matter?

Dr. Bloom:
So the term oligomer refers to an aggregate of two or more molecules, and so the smallest tau oligomer would be a dimer, two tau molecules tightly associated with each other. As these oligomers or as a dimer adds another subunit, it becomes a trimer, so on and so forth, and depending upon how these subunits are arranged initially, many of these aggregates, as they get larger, take on the appearance of filaments. It's not clear that all oligomers lead to filaments. That's something we just don't know.

So a normal neuronal nucleus looks sort of like a rugby ball. It's an ellipsoid and has a nice smooth surface, but in Alzheimer's disease and in a lot of other neurodegenerative disorders, nuclei in diseased neurons invaginate. They take on the appearance of raisins or prunes. And what we discovered a couple years ago and just published is that if you simply expose neurons in culture to tau oligomers by adding the oligomers to the medium in which the neurons are growing, within an hour their nuclei look like these invaginated nuclei in Alzheimer's brain.

And we looked at a number of other things that might accompany this physical change in the appearance of the nucleus. For one, we found that nucleocytoplasmic transport, the movement of materials between the cytoplasm and the nucleus, is disrupted, and that's because the structures that regulate this transport, nuclear pore complexes, are somehow damaged. We found that within hours after exposure of these neurons to extracellular tau oligomers, there's a lot of changes in gene expression. And the one that's most notable is the expression of the tau gene itself, which seems to be upregulated about three-fold, and that raises the possibility of a snowball rolling downhill, if you will, that neurons that are exposed to bad tau probably are prompted to make more tau, which just exacerbates the problem.

Dr. Wilner:
How might additional research help people with Alzheimer's disease?

Dr. Bloom:
Well, the biochemical, genetic, cell biological mechanisms of Alzheimer's disease, as a collection are very, very complicated. For a long time, the prevailing wisdom, for example, was that not only are plaques and tangles signs of a diseased brain, but that they are somehow responsible for the symptoms of Alzheimer's disease, and research over the last 20 years or so has indicated that actually, it's these oligomers, not only of tau but of amyloid and amyloid beta, that are doing all this damage behind the scenes. By the time a person becomes symptomatic for Alzheimer's disease, unfortunately, there's already massive irreversible brain damage, and this does occur after plaques and tangles become evident, but there's a lot of damage that occurs before the appearance of plaques and tangles.

Dr. Wilner:
Well, before we close, Dr. Bloom, anything you'd like to add?

Dr. Bloom:
I just hope that the public stands behind this effort that has been growing steadily to find a cure—actually, not a cure for Alzheimer's disease. We're not going to be able to cure people who are already symptomatic. The best that we would be able to do in that case is to

slow or maybe bring to a halt further cognitive decline. The answer is going to be prevention; prevention that will begin maybe 15 or 20 years before symptom onset based on biomarker studies. You mentioned a couple, PET imaging, but we're on the cusp of having simple blood tests for Alzheimer's disease. And so we can already identify people who are at high risk long in advance. We just don't how to treat them yet. So that's the next step, is to figure out how to treat them so that the symptoms either never arise or their arrival is delayed and the progression is slowed.

Dr. Wilner:
Well, with those final comments in mind, I want to thank my guest, Dr. George Bloom, for joining me to discuss toxic tau proteins in Alzheimer's disease. Dr. Bloom, it was a pleasure having you on the program.

Dr. Bloom:
Thank you again, Andrew, for inviting me.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.